UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,778	04/14/2006	Tetsuo Ikezono	P26460	9010

7055 7590 05/25/2010

GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
05/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,778	IKEZONO ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-2, 4-13* is/are pending in the application.

4a) Of the above claim(s) *8-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 2/16/2010, is acknowledged and has been entered. Claims 1-2 were amended. Claim 3 was canceled. Accordingly, claims 1-2 and 4-13 are currently pending in the application, with claims 8-13 currently withdrawn. Claims 1-2 and 4-7 are subject to examination below.

Priority

2. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/JP03/08123, filed 6/26/2003, which claims foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 2002-187479, filed on 6/27/2002 in Japan.

Objections/ Rejections Withdrawn

3. The objection to claim 2 has been withdrawn in response to Applicant's amendments thereto.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting a perilymph fistula by detecting the

existence of a 16-kDa N-terminal fragment of Cochlin using an anti-Cochlin N-terminal fragment antibody that recognizes an antigenic determinant contained within amino acids 36 to 127 of SEQ ID NO:1, does not reasonably provide enablement for methods of detecting a perilymph fistula by detecting the existence of any type of Cochlin, or by any means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to methods of using Cochlin as a marker of perilymph fistula. Perilymph (fluid existing in the inner ear tissues) may leak into the middle ear, a pathological condition known as "perilymph fistula" (specification, pages 1 and 9). The specification suggests that the protein Cochlin exists only in the perilymph, such that detection of this protein would indicate the presence of perilymph. In particular, the specification suggests that antibodies directed against portions of the Cochlin protein may be used in order to assay fluid found in the middle ear in order to determine whether the fluid is perilymph (and hence whether perilymph fistula has occurred). See especially pages 1 and 9-10.

The claims recite detecting the existence of "Cochlin". As defined in the specification, the term "Cochlin" refers to a protein encoded by a COCH gene (pages 9-10). In addition to the full-length amino acid sequence of Cochlin, three isoforms of different molecular weight were known (p63, p44, and p40; ibid).

Therefore, the term "Cochlin" as used in the claims would broadly encompass any protein encoded by the COCH gene. As amended instantly, the claims indicate that the Cochlin protein detected consists of either an N-terminal fragment of a p63 isoform of Cochlin; or

alternatively a 16kDa N-terminal fragment of Cochlin that is recognized by an anti-Cochlin N-terminal fragment antibody.

The prior art recognized that protein products of the COCH gene are found in the inner ear. See Ikezono et al. (Biochimica et Biophysica Acta 1535 (2001) 258-265), which reports the detection of Cochlin in inner ear tissue samples (see in particular the abstract; page 259, section 2.1; and page 264, right column, penultimate paragraph). Similarly, Botstein et al. (US 6,913,919 B2) taught that Cochlin (Coch-B2) is specifically expressed in the inner ear. See column 12, line 60 to column 13, line 10. Ikezono et al. also recognized that Cochlin exists in the inner ear as different isoforms, identified as p63, p44, and p40 (see page 264, left column; and also Tables 1-3 and Figure 4).

Nonetheless, the prior art failed to specifically teach that Cochlin exists in perilymph fluid (Ikezono et al. 2001 studied homogenized *tissue* samples).

However, it was also known that proteins may penetrate into the perilymph. See Magal et al. (US 6,274,554 B1) at column 20, lines 45-48.

Armed with such knowledge, one of ordinary skill in the art may reasonably expect that Cochlin, as an inner ear protein, would penetrate into perilymph (see the Office action mailed 4/29/2009 at pages 4-7 and 10-13).

However, in the instant case there is evidence of substantial unpredictability. In particular, Ikezono et al. ("Cochlin-Tomoprotein: A Novel Perilymph-Specific Protein and a Potential Marker for the Diagnosis of Perilymphatic Fistula" Audiol Neurotol 2009;14:338-344; submitted as part of Applicant's Reply of 7/28/2009, copy attached herewith) detected the three Cochlin isoforms p63, p44, and p40 in inner ear tissue. However, when perilymph was analyzed,

only a distinct isoform, the 16-kDa isoform termed "Cochlin-Tomoprotein", was detected (see entire selection, in particular page 338, "Background").

Similarly, Applicants have elsewhere reported that while this 16-kDa isoform is found in perilymph, other known Cochlin isoforms cannot be detected in perilymph. See Ikezono et al. ("Identification of a novel Cochlin isoform in the perilymph: insights to Cochlin function and the pathogenesis of DFNA9" Biochemical and Biophysical Research Communications 314 (2004) 440–446), in particular the abstract; paragraph bridging pages 440-441; Figure 1A; page 443, right column; page 444, left column). The authors discuss how the N-terminal portion of full-length Cochlin is likely cleaved to form the Cochlin-Tomoprotein isoform, which is then secreted into the perilymph; and further comment that it is unlikely that full-length Cochlin is processed in the perilymph. See page 445, left column.

The evidence of record therefore suggests that none of the three Cochlin isoforms identified in the prior art are present in perilymph. Rather, the form of Cochlin that is found in perilymph is a previously-unidentified isoform having an approximate molecular weight of 16 kDa and corresponding approximately to residues 32-132 of Cochlin (Ikezono et al. 2009, Figure 1).

In view of this unpredictability, it is apparent that one of ordinary skill in the art would face an undue burden of experimentation in carrying out the claimed invention in its full scope. In particular, Applicant's postfiling publications indicate that only a single Cochlin isoform is actually present in perilymph, namely the 16-kDa N-terminal fragment now known as Cochlin-Tomoprotein. By contrast, the claims broadly encompass detection of perilymph fistula by detecting a genus of molecules. In particular, the claims encompass detection of any N-terminal

fragment of the p63 isoform of Cochlin. However, the identities of such fragments cannot be envisaged based on the specification, as it is not disclosed which fragments of p63 exist in perilymph. It is not disclosed, for example, what the particular N-terminal fragments are and what their amino acid sequences are.

As would be appreciated by the skilled artisan, molecules not present in perilymph would not be useful markers in methods for detecting perilymph fistula. Applicant's postfiling data indicate that not all Cochlin molecules do not exist in perilymph (Ikezono et al. 2009, see especially Figure 1; Ikezono et al. 2004, abstract). In view of this unpredictability, it cannot be ascertained based on the specification which molecules falling within the claimed genera actually exist in perilymph and therefore possess the functional characteristics necessary for the claimed method.

Regarding the guidance presented in the specification, it is noted that the specification discloses immunological methods for detecting Cochlin in perilymph, in which antibodies that recognize antigenic determinants contained within amino acids 36-127 of full-length Cochlin (SEQ ID NO:1) were used to detect Cochlin. Such antibodies would be capable of binding to the 16-kDa Cochlin-Tomoprotein isoform found in perilymph, as this isoform includes residues 36-127 of SEQ ID NO:1 (Ikezono et al. 2009, Figure 1). Using these antibodies, Applicants successfully detected a protein of 16 kDa existing only in perilymph (Example 1).

However, the specification fails to provide guidance with regard to how to detect any other Cochlin molecules as markers of perilymph fistula. There are no working examples in which any other Cochlin molecules were detected in perilymph.

In addition, while the level of skill in the art was high, Applicants have argued that the knowledge in the art regarding markers for diagnosis of perilymph fistula was low even well after the filing date of the instant invention. See the Reply of 7/28/2008 at page 16, second paragraph; and also at Ikezono et al. 2009, in particular at page 339, left column ("To date, there is no clinically relevant biochemical marker for perilymph leakage" and also at page 341, left column ("There is no established diagnostic test with enough sensitivity and specificity to identify the presence or absence of perilymph leakage").

In summary, while the prior art recognized Cochlin to be an inner ear protein, its secretion into perilymph fluid had not been previously reported. Further, there is evidence of substantial unpredictability in regards to this secretion, insofar as none of the previously-known Cochlin isoforms are apparently released into perilymph. Rather, Applicant's data in the specification and in the postfiling literature indicate that only the 16-Kda Cochlin-Tomoprotein isoform (which was not previously known) is actually present is perilymph. Such data involving the detection of a single Cochlin fragment cannot be extrapolated to the genus of molecules now claimed, as it cannot be envisaged based on the specification what other Cochlin fragments might also exist in perilymph.

When taken together with the breadth of the claims, which encompass detection of a genus of Cochlin molecules in perilymph, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without undue experimentation.

Response to Arguments

6. Applicant's arguments filed 2/16/2010 with respect to the rejections under § 112, 1st paragraph (scope of enablement) have been considered but are not found persuasive.

Applicant argues that the specification provides sufficient guidance such that one of skill in the art could make and use the claimed invention without undue experimentation (Reply, page 6).

Such assertions of a general nature do not specifically address the grounds on which the rejections were made, and are therefore not in compliance with 37 CFR 1.111 as they do not distinctly and specifically point out the supposed errors in the examiner's action.

Applicant also points to the instant amendments to the claims; however, for reasons of record the scope of the claimed subject matter is not commensurate in scope with the teachings of the specification.

Applicant further argues that the instant specification as well as a postfiling publication by Applicants show detection of a 63 kDa isoform that is found in perilymph (Reply, page 7).

This is not found persuasive because the claims recite detection of *an N-terminal fragment* of a p63 isoform of Cochlin, and not detection of the p63 isoform *per se*. Whether the 63 kDa isoform itself is found in perilymph is therefore tangential to the issue of whether the specification enables one of ordinary skill in the art to detect N-terminal fragments of this isoform.

Similarly, with respect to Applicant's arguments that claims 6-7 encompass detection of the p63 isoform as well as a 16 kDa N-terminal fragment (Reply, page 7), the examiner notes that the claims do not invoke detection of the p63 isoform but rather of a genus of fragments

thereof. In addition, it appears that Applicant perceives claim 7 to be directed to detection of the p63 isoform. However, Applicant is reminded that as claim 7 employs open transitional language in reference to the indicated amino acid sequences, the claim is not limited to detection of any particular fragment. See, e.g., the Office action mailed 10/30/2008 at page 12.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

5/20/10